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Abstract: The impact of intraocular involvement (IOL) in primary CNS lymphoma (PCNSL) has not been sufficiently evaluated. Here, we present the analysis of IOL in the only completed randomized phase III trial in PCNSL. The G-PCNSL-SG1 study evaluated the role of whole-brain radiotherapy in primary therapy of PCNSL. Data of the 526 eligible study patients were checked, and clinical characteristics, therapy, and outcome of patients with IOL diagnosed at study inclusion were analyzed. Ophthalmologic examination at study inclusion was performed in 297 patients (56.5 %) of whom IOL was diagnosed in 19 (6.4 %). Clinical characteristics did not significantly differ between patients with IOL (IOL+) and those without (IOL-). The median progression-free survival (PFS) in the IOL+ group was 3.5 months (95 % CI 0.0-7.07) as compared to 8.3 months (95 % CI 4.78-11.78) in the IOL- group (P = 0.004), the median overall survival (OS) was 13.2 months (95 % CI 0.86-25.62) and 20.5 months (95 % CI 15.56-25.5), respectively (P = 0.155). In multivariate analysis, a significantly inferior PFS and OS for IOL+ patients were found. IOL at diagnosis of PCNSL was an independent negative prognostic indicator for PFS and OS in this analysis.

DOI: https://doi.org/10.1007/s00277-014-2212-z

Originally published at:
Kreher, S; Strehlow, F; Martus, P; Roth, P; Hertenstein, B; Röth, A; Birnbaum, T; Griesinger, F; Rauch, M; Kanz, L; Thiel, E; Weller, M; Korfel, A (2015). Prognostic impact of intraocular involvement in primary CNS lymphoma: experience from the G-PCNSL-SG1 trial. Annals of Hematology, 94(3):409-414.
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Prognostic impact of intraocular involvement in primary CNS lymphoma: experience from the G-PCNSL-SG1 trial

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Running title: Prognostic impact of intraocular involvement in primary CNS lymphoma

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Authorship and Disclosures: MW, ET and AK were the principal investigators; PR, BH, AR, TB, FG, MR, MW, ET and AK contributed patients to the trial; PM did the statistical analyses; SK, FS and AK wrote the report and all authors approved the report. The authors report no potential conflicts of interest.

Key words: intraocular lymphoma, primary CNS lymphoma, progression-free survival, overall survival

Word count 2927

Abstract:

Background: The impact of intraocular involvement (IOL) in primary CNS lymphoma (PCNSL) has not been sufficiently evaluated. Here, we present the analysis of IOL in the only randomized phase III trial in PCNSL. **Methods:** The G-PCNSL-SG1 study evaluated the role of whole-brain radiotherapy in primary therapy of PCNSL. Data of the 526 eligible study patients were checked, and clinical characteristics, therapy and outcome of patients with IOL diagnosed at study inclusion were analyzed. **Results:** Ophthalmologic examination at study inclusion was performed in 297 patients (56.5%) of whom IOL was diagnosed in 19 (6.4%). Clinical characteristics did not significantly differ between patients with IOL (IOL+) and those without (IOL-). The median progression-free survival (PFS) in the IOL+ group was 3.5 months (95% CI 0.0-7.07) as compared to 8.3 months (95% CI 4.78-11.78) in the IOL- group (P = 0.004), the median overall survival (OS) was 13.2 months (95% CI 0.86-25.62) and 20.5 months (95% CI 15.56-25.5), respectively (P = 0.155). In multivariate analysis, a significantly inferior PFS and OS for IOL+ patients were found.

Conclusions: IOL at diagnosis of PCNSL was an independent negative prognostic indicator for PFS and OS in this analysis.

Introduction

Primary CNS lymphoma (PCNSL) usually presents as an intracerebral mass but may also show concomitant meningeal or intraocular dissemination[1]. Intraocular involvement (IOL) of PCNSL is a rare condition, which may occur before PCNSL is diagnosed, concomitantly with the PCNSL diagnosis, or at relapse. The localization may include vitreous, retina or optic nerve head. The spectrum of clinical symptoms varies from asymptomatic patients (up to 40%) to symptoms of chronic uveitis masquerade syndrome such as blurred vision and floaters up to complaints of red eye, photophobia, and ocular pain[2-5]. Bilateral involvement is common and occurs in almost 80% of cases[2]. The diagnosis is made by ophthalmologic examination where typically vitreitis or multifocal yellow-coloured subretinal infiltrates are seen. The cytologic confirmation in the vitreous is often confounded by the presence of reactive immune cells, necrotic cells, debris, and fibrin. In cytologically negative cases, chorioretinal biopsy can be performed at specialized centers, revealing tumor cell infiltrates between the retinal pigment epithelium and Bruch's membrane, perivascular clumps of tumor cells in the retina and optic nerve head, diffuse infiltration in the vitreous, and hemorrhagic retinal necrosis[6]. Due to the extreme rarity of this condition, data on therapy and prognostic impact of IOL diagnosed concomitantly with PCNSL is very scarce. As a consequence the optimal therapy for IOL has not been established. Systemic chemotherapy with high-dose methotrexate (HDMTX) sometimes amended by ocular radiotherapy or ocular chemotherapy or rituximab instillation is currently being performed at most centers. The prognostic impact of IOL has not been sufficiently evaluated either. A few small and retrospective studies with heterogeneous treatment protocols failed to observe a significant difference in outcome of patients with IOL (IOL+) versus those without (IOL-)[7-9]. In the present analysis, we evaluate the impact of IOL on outcome of PCNSL patients treated within the G-PCNSL-SG1 trial[10].

Methods:

Patients and treatment

As previously reported[10], 526 eligible patients with newly diagnosed PCNSL were enrolled at 75 centers and treated between May 2000 and May 2009. Major inclusion criteria were: immunocompetent adult patients with histologically or cytologically (in cerebrosponal fluid (CSF)) confirmed PCNSL, Karnofsky performance score (KPS) >30 when due to PCNSL or >50 when due to other conditions, creatinine clearence ≥50 ml/min and written informed consent. Clinical staging work-up included physical examination, mini mental status examination, biochemical serum profile, serological assessment for HIV and hepatitis B and C infection, brain MRI (CT when MRI was not available or possible), CT scans of chest and abdomen, bone marrow biopsy and CSF examination. Ophthalmologic assessment including slit-lamp examination was part of the staging work-up. Patients without initial slit-lamp examination were not excluded from trial participation. Patients were

randomly allocated to receive first-line chemotherapy based on HDMTX with or without subsequent whole-brain radiotherapy (WBRT), with stratification by age (<60 versus ≥60 years) and institution (Berlin versus Tübingen versus all other sites). Between May 2000 and August 2006, study therapy consisted of HDMTX (4 g/m^2 as a 4-h i.v. infusion with dose reduction according to creatinine clearence) on day 1 of six 14-day cycles; thereafter, patients were to receive HDMTX plus ifosfamide 1.5 g/m^2 on days 3–5 of six 14-day cycles. Addition of ifosfamide was a protocol amendment based on increasing awareness that HDMTX alone might be an insufficient first-line chemotherapy. In those assigned to receive first-line chemotherapy followed by radiotherapy, WBRT was to be given at a total dose of 45 Gy in 1.5 Gy fractions. Patients within the WBRT randomization group who had ocular involvement at study inclusion were to receive WBRT with inclusion of both orbits up to 30 Gy. Patients allocated to first-line chemotherapy without WBRT who had not achieved complete response (CR) were given high-dose cytarabine (HDAraC), 2 × 3 g/m^2 on days 1–2 of 22-day cycles, and did not receive any further eye-dedicated therapy.

The study protocol was approved by local institutional review boards or ethical review committees. All participants gave written informed consent.

Statistics

For statistical analysis, patient pre-therapeutic characteristics were grouped according to prognostic factors previously published: age, Karnofsky Performance Score (KPS), the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (class 1 patients <50 years, class 2 patients ≥50 and KPS ≥ 70, class 3 patients ≥50 and KPS < 70)[9], lactate dehydrogenase (LDH) in serum, number of brain lesions (0–1 and ≥2). The tests of significance were carried out between IOL+ and IOL- patients. Progression-free survival (PFS) was defined as the time from study entry to first progression or death from any cause. Overall survival (OS) was defined as the time from study entry to death. PFS and OS were estimated by the Kaplan–Meier method. Group comparisons were carried out using the log-rank test. Distribution of patients' characteristics to different groups was analyzed by the chi-square test. Mean values of independent groups were compared with Student's t-test. The level of significance was 0.05 (two-sided). In the multivariate analysis backward variable selection was applied. Two-sided 95% confidence intervals are presented. Commercially available software was used (SPSS for Window, release 18.0).

Results

Patient characteristics

Of 526 eligible patients, 297 (56.5%) underwent ophthalmologic assessment within initial staging work-up. Among them, 19 patients (6.4%) had concomitant IOL on the slit-lamp examination. In 9 of

these patients, IOL was further analyzed by cytomorphologic examination of vitreous aspirate with evidence of lymphoma cells in 8 patients and suspicious but inconclusive cytology in 1 patient. The main characteristics of IOL+ patients and the comparison with IOL- and all eligible study patients are summarized in Table 1. The comparison with patients without slit-lamp examination is given in Supplementary Table 1. No significant differences between these groups were observed for any parameter.

Treatment and response

Of the 19 IOL+ patients, 14 (73.7%) were treated with HDMTX monotherapy and 5 additionally received ifosfamide (Table 2). After HDMTX-based treatment 4 patients (21%) were in CR and did not receive further treatment. Fifteen patients failed to achieve CR: 4 (21%) had partial remission, one patient had stable disease, 9 (47%) had progressive disease and one patient had an unknown remission status (Table 2). The differences with respect to first-line chemotherapy and response between IOL+ and IOL- patients were not significant. Among patients who failed to achieve a CR to HDMTX-based treatment, 7 received WBRT (5 with ocular radiotherapy [RT]), 3 HDAraC, and 5 had a rapid progressive disease with poor performance status that excluded further treatments. After the total primary treatment 8 (42%) of 19 IOL+ patients achieved an objective response, which was complete in 7 cases (37%).

Salvage treatment was not part of the study treatment. In the IOL+ group, two patients received systemic chemotherapy and 5 patients received systemic chemotherapy (one with additional intravitreal injection of MTX) plus WBRT (two with ocular radiotherapy (RT)). All patients treated with salvage WBRT had not received WBRT as part of initial treatment and were thus not irradiated twice.

Survival outcome

The median follow-up of all patients who underwent ophthalmologic assessment was 78.4 months. The median PFS (Table 2 and Figure 1) in the IOL+ group was 3.5 months (95% CI 0.0-7.07), as compared to 8.3 months (95% CI 4.78-11.78) in the IOL- group (P = 0.004). Sites of progression or first relapse in IOL+ patients included brain in 12 patients (63%), eyes in 1 (5%), brain and eyes in 1 (5%), meninges in 1 (5%) and was undetermined in 4 (21%). Both ocular relapses occurred within two months after completion of HDMTX-based chemotherapy. One patient showed an isolated intraocular relapse after an initial CR, the second patient had a partial response and rapidly progressed with concomitant intracerebral and intraocular involvement. In the IOL- group, 8 (2.8%) patients relapsed with IOL. The median OS in the IOL+ group was 13.2 months (95% CI 0.86-25.62) versus 20.5 months (95% CI 15.56-25.5) in the IOL- group (P = 0.155). In multivariate analyses, after adjustment

for age and KPS as the most important risk factors in PCNSL, we found a significantly inferior PFS (HR 2.18; $P = 0.003$) and OS (HR 2.17; $P = 0.004$) for IOL+ patients (Table 3).

Discussion

This is the first analysis of IOL in PCNSL in an adequately sized cohort treated within a prospective trial with HDMTX-based chemotherapy.

The frequency of IOL in this study of 6.5% is within the range of 1-19% reported in prospective PCNSL patients` series[11-15]. The high range of IOL frequency reported is most probably due to a high proportion of asymptomatic patients and challenges in diagnosing this condition even for trained ophthalmologists. Efforts to improve the diagnostic accuracy include flow cytometry and determination of cytokine levels in the vitreous body[16,17]. However, these procedures are currently neither standardized nor commonly available for PCNSL staging.

We did not observe any association between IOL and any other patients´ characteristics documented in the G-PCNSL-SG1. Particularly, there was no association with positive CSF cytology status that was previously described[7]. In fact, only one of our 19 IOL+ patients had concomitant meningeal dissemination, in contrast to 20 – 33% of IOL+ patients reported in the literature[6,9]. Moreover, we did not find serum LDH elevation more frequently in IOL+ patients[6].

This study is the first to demonstrate that IOL at diagnosis of PCNSL is an independent negative prognostic indicator both for PFS and OS. For PFS we found unambiguous results with relevant and significant hazard ratios both in univariate and multivariate analyses. For OS, after adjustment for KPS and age, we detected a significant hazard ratio of 2.2 in multivariate analysis for IOL+. The univariate analysis revealed a non-significant result which can be explained by a higher proportion of younger patients with better KPS in IOL+ as compared to IOL$^-$.

All previous analyses showing no prognostic impact of IOL in PCNSL were performed, as the present trial, in retrospectively analysed series, however, with more heterogeneously treated patients. In the three larger (n>10) series the outcome of IOL+ patients was comparable to that of IOL- and superior to that in the present study with median PFS of 18 months[2] and median OS of 20-31 months[2,7,18]. This cannot be explained by differences in patients` age or performance status between those analyses and the present study. Moreover, HDMTX considered the most important treatment in PCNSL was given to all patients in our series but only to 55-84% of patients in the other series, whereas WBRT was part of treatment in 37% of our patients and 33-71% of patients in the other series, respectively. The frequency of ocular RT was, however, higher in the previous series with 45-64% as compared to 26% in our series, and it remains unclear if this has contributed to the better outcome.

IOL could reflect a higher tumor burden in PCNSL or a more aggressive tumor behaviour. Another hypothesis concerning the worse prognosis of IOL+ patients could be the involvement of a compartment that is difficult to treat. Previous analyses described difficulties in achieving therapeutic concentrations of MTX in the vitreous humor which may result in the development of a sanctuary from where surviving tumor cells may lead to a relapse. The higher rate of ocular relapse in IOL+ patients of 21-33%[2,7,18] as compared to IOL- patients would support this hypothesis. The relatively low rate of ocular relapse found in the present series despite lower frequency of eye-dedicated treatment as compared to retrospective analyses[2,7,18] could be explained by the lack of routine ophthalmologic examination during follow-up in the G-PCNSL-SG1 trial.

Only 57% of patients from the G-PCNSL-SG1 study received an ophthalmologic evaluation which represents the major weakness of this analysis. Nevertheless, we do not think that our results were biased by patients` selection, since major clinical characteristics and outcome of patients who did not receive ophthalmologic examination were similar to those of examined patients (Table 1 and Supplementary Table 1).

Our findings underline the importance of detailed ophthalmologic assessment even in asymptomatic PCNSL patients as recommended by the guidelines of the International Primary CNS Lymphoma Collaborative Group[21], and suggest that these patients should be evaluated and treated as high-risk population. HDMTX alone might not be an appropriate treatment for these patients, and more aggressive therapy up to high-dose chemotherapy with stem-cell transplantation should be considered in those who can tolerate it. Whether an additional eye-dedicated treatment such as local RT or intravitreal injection of chemo-/immunotherapeutics[19,20] can improve the prognosis of IOL+ PCNSL patients remains unclear[2]

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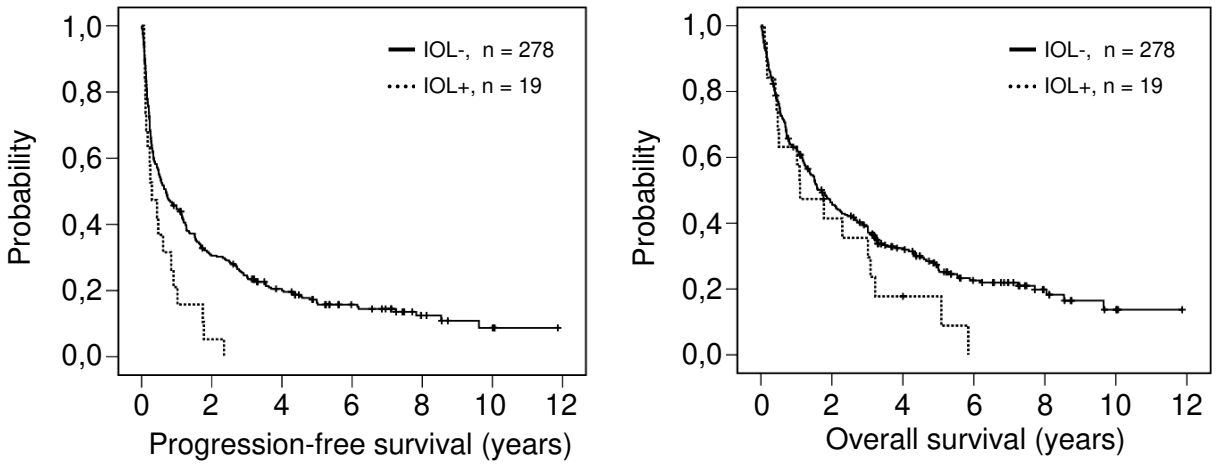
Figure1

Figure 1: Progression-free survival and overall survival in patients with intraocular involvement (IOL+) versus those without (IOL-).



Supplementary table 1

Click here to download Supplementary Material: Kreher_TableS1.doc

Table 1: Comparison of clinical characteristics of patients with intraocular involvement (IOL+) versus those without (IOL-).

Characteristics	IOL+ (n=19) n (%)	IOL- (n=278) n (%)	All patients (n=526) n (%)	*P* value (IOL+ versus IOL-)
Age (years) Median (range)	61 (46-76)	64 (19-84)	63 (19-84)	0.279
Male/female	14/5	153/125	299/227	0.152
KPS, mean	74	70	70	0.477
MSKCC score				
1	1 (5.3%)	42 (15.1%)	84 (15.9%)	0.284
2	11 (57.9%)	126 (45.3%)	218 (41.4%)	
3	4 (21%)	88 (31.6%)	150 (28.5%)	
Not recorded	3 (15.8%)	22 (7.9%)	74 (14.0%)	
Serum LDH elevated	2 (10.5%)	69 (24.8%)	109 (20.7%)	0.1
Not recorded	0	19 (6.8%)	229 (43.5%)	
Meningeal involvement	1 (5.2%)	7 (2.5%)	17 (3.2%)	0.403
Not recorded	4 (21.0%)	49 (17.6%)	161 (30.6%)	
Number of cerebral lesions				
0-1	7 (36.8%)	137 (49.3%)	262 (49.8%)	0.281
≥2 lesions	8 (42.1%)	85 (30.6%)	169 (32.1%)	
Not recorded	4 (21.0%)	56 (20.1%)	95 (18.0%)	

KPS, Karnofsky Performance Score; MSKCC, Memorial Sloan-Kettering Cancer Center; LDH, lactate dehydrogenase

Table 2: Treatment, objective response to HDMTX-based chemotherapy and outcome of patients with intraocular involvement (IOL+) versus those without (IOL-).

Characteristics	IOL+ (n=19) n (%)	IOL- (n=278) n (%)	*P* value
HDMTX versus HDMTX/IFO	14 (73.7%) 5 (26.3%)	208 (74.8%) 70 (25.2%)	0.549
WBRT	10 (52.6%)	140 (50.3%)	0.848
Response to HDMTX-based chemotherapy			
Complete response	4 (21.1%)	103 (37%)	0.289
Partial response	4 (21.1%)	58 (20.9%)	
Stable disease	1 (5.2%)	12 (4.3%)	
Progressive disease	9 (47.4%)	74 (26.6%)	
Not recorded	1 (5.2%)	31 (11.1%)	
Median PFS (months)	3.5 (95% CI: 0.0-7.1)	8.3 (95% CI: 4.8-11.8)	0.004
Median OS (months)	13.2 (95% CI: 0.9-25.6)	20.5 (95% CI: 15.6-25.5)	0.155

HDMTX, high-dose methotrexate; IFO, ifosfamide; WBRT, whole-brain radiotherapy; PFS, progression-free survival; OS, overall survival

Table 3: Univariate and multivariate analyses for progression-free survival and overall survival.

	Progression-free survival			Overall survival		
	Hazard ratio	**95% CI**	**p value**	**Hazard ratio**	**95% CI**	**p value**
Univariate analysis						
IOL+	1.96	1.22-3.15	0.005	1.43	0.87-2.35	0.16
age*	1.44	1.19-1.76	<0.001	2.00	1.61-2.49	<0.001
sex‡	0.97	0.80-1.16	0.72	1.02	0.83-1.24	0.87
KPS†	1.14	1.08-1.20	<0.001	1.19	1.12-1.25	<0.001
LDH#	1.33	1.03-1.71	0.029	1.32	1.01-1.72	0.042
Multivariate analysis						
IOL+	2.18	1.30-3.66	0.003	2.17	1.29-3.66	0.004
age*		not significant, p = 0.40		1.68	1.24-2.27	0.001
sex‡		not significant, p = 0.99			not significant, p = 0.84	
KPS†	1.18	1.10-1.26	<0.001	1.20	1.12-1.29	<0.001
LDH#		not significant, p = 0.057			not significant, p = 0.064	

*Age of 60 years or older versus younger than 60 years. ‡Female sex versus male sex. †10% decrease in Karnofsky Performance Score. #Elevated serum lactate dehydrogenase (LDH) versus normal.